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Filed : May 3, 2002

REMARKS

Claims 1-5 are presented for examination. Applicants thank the Examiner for the review of the instant application, and withdrawing the objection to the specification. Applicants acknowledge the Examiner's withdrawal of the rejection of Claims 1-5 under 35 U.S.C. § 103(a) as being obvious over Fujikawa-Adachi *et al.* The rejections of the presently pending claims are respectfully traversed.

Rejection Under 35 U.S.C. §101 – Utility

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking utility for the reasons set forth on pages 3-4 of the previous Office Action. The PTO asserts that the data of Example 18 are insufficient because "[t]here is no guidance in the specification as to how high the levels are," and the first Grimaldi declaration "does not teach the level of reproducibility or the level of reliability of the results." Office Action at 4. The PTO also states that "[n]either the specification nor the declarations provide any evidence that indicates what the differences were or whether the results were statistically significant." Office Action at 4. The PTO asserts that Applicants have provided "no indication of the nature or number of samples that were used. In addition, one cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates." Office Action at 4. The PTO concludes that the disclosure "does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any disease." Office Action at 4.

The PTO also argues that unlike the examples cited in the Grimaldi declaration, "[n]o mutation or translocation of PRO1335 has been associated with stomach, lung, rectal, or skin cancer." Office Action at 4. The PTO concludes that in the absence of any of the above information, the disclosure is insufficient to meet the utility requirement.

Finally, the PTO states that whether or not increased levels of PRO1335 mRNA correlate with increased levels of PRO1335 protein is not an issue. The PTO concludes that the declarations and cited references do not establish a substantial utility for the claimed PRO1335 nucleic acid molecules (presumably the PTO meant claimed antibodies).

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Utility – Legal Standard

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ

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885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

[T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be “*reasonably* indicative of the desired [pharmacological] response.” In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a

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therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art “to a reasonable probability.” In addition, the evidence need not be direct, so long as there is a “sufficient correlation” between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

[I]n *vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is “an invariable exact correlation” between gene expression and protein expression. Instead, Applicants’ position detailed below is that a measured change in gene expression in cancer cells establishes a “significant probability” that the expression of the encoded polypeptide in cancer will also be changed based on “a reasonable correlation therebetween.”

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the

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evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly stomach, lung, rectal, and skin cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1335 polypeptide is more highly expressed in normal stomach, lung, rectal, and skin tissue compared to stomach, lung, rectal and melanoma tumor, respectively;
2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;
3. Given Applicants' evidence that the level of mRNA for the PRO1335 polypeptide is decreased in stomach, lung, rectal and melanoma tumor, compared to normal tissue counterparts, it is likely that the PRO1335 polypeptide is differentially expressed in stomach, lung, rectal and melanoma tumors;
4. The claimed antibodies to PRO1335 polypeptides therefore have utility as diagnostic tools for cancer.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it does not allow a skilled artisan to differentiate amongst expression levels in order to diagnose any disease;

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2. The PTO argues that because no mutation or translocation of PRO1335 has been associated with stomach, lung, rectal, or skin cancer, the disclosure is insufficient to meet the utility requirement;

3. Finally, the PTO states that whether or not increased levels of PRO1335 mRNA correlate with increased levels of PRO1335 protein is not an issue.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, the fact that no mutation or translocation of PRO1335 has been associated with stomach, lung, rectal, or skin cancer does not prevent its use as a diagnostic tool for certain cancers. Third, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1335 protein is likely differentially expressed in certain tumors. This provides utility for antibodies to the PRO1135 proteins as cancer diagnostic tools. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, to a **reasonable probability**, that the asserted utility is true. As stated above, Applicants’ evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO1335 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO’s argument that the evidence of differential expression of the gene encoding the PRO1335 polypeptide in stomach, lung, rectal and melanoma tumors is insufficient.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1335 was more highly expressed in normal stomach, lung, rectal, and skin tissue compared to stomach, lung, rectal and melanoma tumor, respectively. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA

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libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1335 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, Applicants previously submitted as Exhibit 1 a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest “can be used to differentiate tumor from normal.” He explains that, contrary to the PTO’s assertions, “The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue.” (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, “If a difference is detected, this indicates that the gene and its corresponding

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polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor.”

The PTO has stated that the Grimaldi Declaration is insufficient to overcome the rejection of Claims 1-13. The PTO argues that Example 18 is insufficient because it does not teach how high the expression level is, what the level of reproducibility or reliability is, whether the results are statistically significant, or the nature or number of samples that were used. The PTO also argues that one cannot determine if the observed “amplification” is due to an increase in chromosomal copy number or an increase in transcription rates. The PTO concludes that the disclosure would not enable one of skill in the art to differentiate amongst expression levels to diagnose any disease.

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that “[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned.” PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as “opinions” without an adequate explanation of how the declaration fails to rebut the Examiner’s position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

In addition, Applicants provide herewith as Exhibit 1 a copy of page 122 of the 2002-2003 New England Biolabs catalog. Exhibit 1 shows DNA size markers of differing lengths run on an agarose gel. The column on the left provides the mass of each marker in nanograms and the column on the right provides the length of the marker. It is apparent that the band intensity of markers having mass differences of two-fold are readily distinguishable by eye (*see e.g.*, the difference in band intensities of the 0.1kb fragment present at 61ng and the 0.5kb marker present at 124ng). Accordingly, Applicants maintain that the procedures used to detect differences in expression levels were sufficiently sensitive to detect two-fold differences.

The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept

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Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue. Finally, Applicants submit that whether this differential expression is due to an increase in chromosomal copy number or increased transcription rates is not relevant to whether the difference in expression can be used to distinguish tumor from normal tissue.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1335 cDNA between stomach, lung, rectal and melanoma tumor tissue and the normal stomach, lung, rectal and skin tissue, respectively. Therefore, it follows that expression levels of the PRO1335 gene can be used to distinguish stomach, lung, rectal and melanoma tumor tissue from their normal tissue counterparts. The PTO has not offered any significant arguments or evidence to the contrary.

As Applicants explain below, it is more likely than not that the PRO1335 polypeptide is also differentially expressed in stomach, lung, rectal and melanoma tumor tissue, and can therefore be used to distinguish stomach, lung, rectal and melanoma tumor tissue from normal tissue counterparts. This provides utility for the claimed antibodies to the PRO1335 polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1335 polypeptide in stomach, lung, rectal and melanoma tumor, it is more likely than not that the PRO1335 polypeptide is differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

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In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 2). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 3), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 2) and (4th ed. 2002) (submitted herewith as Exhibit 3)). Figure 9-2 of Exhibit 2 shows the steps at which eukaryotic gene expression can

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be controlled. The first step depicted is transcriptional control. Exhibit 2 provides that “[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized.” Exhibit 2 at 403 (emphasis added). In addition, the text states that “Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made.” Exhibit 2 at 453 (emphasis added). Thus, as established in Exhibit 2, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 3, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that “a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA.*” Exhibit 3 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 3 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, “the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes.” Exhibit 3 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, “[f]or most genes transcriptional controls are paramount.” Exhibit 3 at 379 (emphasis added).

Further support for Applicants’ position can be found in the textbook, *Genes VI*, (Benjamin Lewin, *Genes VI* (1997)) (submitted herewith as Exhibit 4) which states “having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription.” *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, *World Journal of Surgical Oncology* 2:13, 2004, submitted herewith as Exhibit 5. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed “a high degree of correlation between

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PSCA protein and mRNA expression” Exhibit 5 at 6. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that “it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA.” Exhibit 5 at 11. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that “PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor.” *Id.*

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 6, states the following:

The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

In response to the second Grimaldi Declaration and the Polakis Declaration, the PTO makes two arguments. First, the PTO states that unlike Her2/Neu and t(5;14) discussed in the second Grimaldi declaration, “[n]o mutation or translocation of PRO1335 has been associated with stomach cancer, lung cancer, rectal cancer, or melanomas.” Office Action at 4. The PTO concludes that in the absence of any of the above information, the disclosure is insufficient to meet the utility requirement. Second, the PTO states that whether or not increased levels of PRO1335 mRNA correlate with increased levels of PRO1335 protein is not an issue.

Applicants submit that a lack of known role for PRO1335 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of

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PRO1335 is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1335 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See, e.g.,* U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 attached hereto as Exhibits 7-10.)

As discussed above, Applicants respectfully disagree with the PTO's position that whether or not increased levels of PRO1335 mRNA correlate with increased levels of PRO1335 protein is not an issue. Because it is more likely than not that the PRO1335 protein is also differentially expressed in certain tumors, antibodies to the protein can be used as a diagnostic tool for cancer.

Thus, the PTO's rejection of the second Grimaldi Declaration and Polakis Declaration because they are viewed as insufficient or irrelevant is misplaced. Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1335 mRNA is more highly expressed in normal stomach, lung, rectal, and skin tissue compared to stomach, lung, rectal and melanoma tumor, respectively, the PRO1335 polypeptide will have the same expression pattern. This differential expression of the PRO1335 polypeptides makes antibodies to them useful as diagnostic tools for cancer.

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The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that antibodies to a polypeptide differentially expressed in certain tumors can be used as a diagnostic tool. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly stomach, lung, rectal, and skin cancer.

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Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies to PRO1335 polypeptide. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1335 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1335 polypeptide is more highly expressed in normal stomach, lung, rectal, and skin tissue compared to stomach, lung, rectal and melanoma tumor, respectively. These data are strong evidence that the PRO1335 gene and polypeptide are associated with stomach, lung, rectal and melanoma tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1335 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly stomach, lung, rectal and melanoma tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted three arguments to support its conclusion that the differential expression of PRO1335 is not sufficient to establish utility for the claimed antibodies: (1) the PTO has challenged the reliability of the evidence reported in Example 18; (2) the PTO argues that because no mutation or translocation of PRO1335 has been associated with stomach, lung, rectal, or melanoma cancer, the disclosure is insufficient to meet the utility requirement; and (3) the PTO states that whether or not increased levels of PRO1335 mRNA correlate with increased levels of PRO1335 protein is not an issue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative

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difference in expression levels, the disclosed nucleic acids, corresponding polypeptides, and antibodies have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have demonstrated that it is not necessary to know the cause or consequence of the differential expression of PRO1335 nucleic acids and polypeptides in certain tumors in order to use antibodies to the polypeptides as diagnostic tools for cancer.

Third, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that antibodies to polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1335 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

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Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1335 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also rejects Claims 1-5 under 35 U.S.C. § 112, first paragraph, as lacking enablement because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

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CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: March 14, 2005

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